REMARKS

At page 2 & 3 of the Office Action, Claims 58-66 and 69-86 were rejected under 35 USC 112, first paragraph. According to the Examiner, Claims 58-66 and 69-86 are enabling *in vitro* but not the present specification fails to provide sufficient guidance or direction regarding *in vivo* use of the claimed biological materials. Regarding Claims 80 and 81, the Examiner stated that the biological material of the present application would elicit host immune responses. The Examiner stated that the instant specification fails to provide an enabling disclosure for other *in vivo* uses, and thus undue experimentation would be required to use the biological material of the present application

Reconsideration is respectfully requested.

The Examiner has acknowledged enablement *in vitro* biological material according to the present invention, but not *in vivo* biological material. Applicants contend that the instant Specification is sufficiently enabling for the *in vivo* uses contemplated.

Skilled persons in the art of grafts transplants have at their disposal an extensive immunosuppressive armamentarium. See e.g., Goodman & Gilman's: "The Pharmacological Basis of Therapeutics", Ninth Edition, pgs 1294 –1306 (Attachment:A). At pages 1294-1295 it is stated "to transplant tissue from one individual to another, it is necessary to suppress the normal immune response in the recipient to prevent rejection of the "foreign" donor tissue. Over the past thirty years, successful allograft transplantation has been possible due mainly to the availability of effective immunosuppressive agents. Initially these included non specific cytotoxic agents (e.g. azathioprine, cyclophosphamide) and corticosteroids (e.g. prednisone) They subsequently have been joined by cyclosporine and tacrolimus and more recently micophenolate mofetil." Therefore, the skilled persons in allograft transplants of kidney, liver, lung, pancreas, and bone marrow transplantation have utilized prednisone and cyclosporine. Azathioprine has been used in combination with these two agents, particularly in heart and renal transplantation. For acute rejection lymphocyte immunoglobulin, antithymocyte globulin (equine), and the monoclonal antibody muromonab-CD3." Therapeutic dosages are provided therein. The newest agents are a microemulsion formulation of cyclosporin A, sirolimus, and daclizumab (an anti-interleukin-2-receptor antibody).

As further evidence, Applicants submit herewith abstracts and references reporting human and animal studies concerning allograft, but in some cases also, xenograft of cellular

lines and in particular Langerhan' s islet cells and dermal cells wherein most of the aforementioned immunosuppressants are used (Attachment: B).

Early and definitive skin replacement of extensive deep partial and full thickness burns has been reported with clinical use of cyclosporin A for immunosuppression in allogenic split thickness skin graft transplants. (Krupp S et al, Mid-term Results with Cultured Epidermal Autografts, Allogenic Skin Transplants and Cyclosporin A Medication, 20 Burns 15-20 (1994)).

Treatment of IDDM patients undergoing islet, segmental pancreas or whole pancreas allotransplantation with immunosuppressive therapy with cyclosporin, steroids and azathioprine resulted in insulin secretory patterns of islet transplanted patients similar to segmental pancreas transplanted patients and lower than whole pancreas transplanted patients at 3 months, 6 months, and 1, 2, 3 and 4 years.(Secchi A et al, Insulin Secretory Patterns and Blood Glucose Homeostasis After Islet Allotransplantation in IDDM Patients: Comparison With Segmental or Whole Pancreas Transplanted Patients Through a Long Term Longitudinal Study, 77 J Mol Med 133-139 (1999)).

In another study, a combination of leflunomide, cyclosporine, and mycophenolate mofetil prevented rejection of porcine islet-like cell cluster xenografts in the rat for up to 24 days after transplantation.(Wennberg et al, Efficacy of Immunosuppressive Drugs in Islet Xenotransplantation: Leflunomide in Combination with Cyclosporine and Micophenolate Mofetil Prevent Islet Xenograft Rejection in the Pig to Rat Model, 63 Transplantation 1234-1242 (1997)).

Rats were grafted with either Lewis (isografts) or Wistar (allografts) pancreatic islet cells obtained by collagenase digestion. Islets implanted into non immunosuppressed hosts completed revascularization by days 3- 7 after transplantation, as shown by detection of endothelial cells within and surrounding the islets. The identical staining pattern of revascularization was observed in non-immunorejecting allografts as well as in isografts treated with cyclosporine A. (Mendola J. et al, Cyclosporine Does Not Inhibit the Process of Revascularization of Pancreatic Islet Transplantation, 6 Cell Transplant 69- 76 (1997)).

Therefore, clinicians skilled in dermal, liver or pancreas islet cells transplants are knowledgeable of immunosuppressant used therapeutically avoid immunorejection of the specific allogeneic transplanted cells. In view of the foregoing, Applicants believe the *in vivo* presently claimed biological material containing homologous cells is sufficiently described, without the necessity of discussing immunosuppressants.

Additionally, on October 23, 2000 via Amendment, Applicants submitted experiments which provided experimental evidence of cell survival following *in vivo* transplantation in the biological material of the present invention. Experiments conducted in nude mice are extrapolable to graft autologous cells or homologous cells associated with an immunosuppressive therapy. These *in vivo* experimental tests demonstrate that three implanted subcutaneously reconstructed tissue (skin adnexa, liver, and langerhans islets) retain their typical morphology three weeks from implantation. The implant was vascularized with new vessels originating from the surrounding tissues with simultaneous degradation of the hyaluronic acid ester scaffolds.

The aforementioned research collectively demonstrates effectiveness of the presently claimed biological material containing autologous and homologous cells when implanted *in vivo*.

Further, Applicant's disagree with the Examiner's opinion that the Specification does not sufficiently disclose the use of the biological material as support for gene transfection since host immune reactions are observed when using autologous cells.

Applicants submit herewith references, where the immune rejection of autologous transfected cells, does not occur (Attachment C).

In one study, retrovirally encoded MyoD 1 cDNA was introduced in autologous dermal fibroblasts of TnI LacZ mice to provoke their conversion into myoblast like cells which were then transplanted into mice. The results indicate that successful implantation of myoblasts obtained from autologous genetically modified fibroblasts is feasible for treating Duchenne's dystrophy.(Huard et al, Transplantation of Dermal Fibroblasts Expressing MyoD1 in Mouse Muscles , 248 Brioche. Biopsy's. Roscommon. 648-654 (1998)).

Using methodology directed to the treatment of Alzheimer's disease, two additional references describe experiments in Rhesus Monkeys following transplant of autologous fibroblasts genetically modified *in vitro* to produce the active ß-subunit of human NGF (see page 1941 right column last paragraph of Conner). (Smith et al, Age Associated Neuronal Atrophy Occurs in the Primate Brain and is Reversible by Growth Factor Gene Therapy , 96 Proc. Natl. Acad. Sic. USA 10893-10896 (1999); Conner J.M. et al, Nontrophic Actions of Neurotrophins: Subcortical Nerve Growth Gene Delivery Reverses Age-Related Degeneration of Primate Cortical Cholinergic Innervation, 98(4) PNAS 1911-1946 (2001).)

In the above references transplantation of autologous cells which underwent a genetic modification did not show immunorejection problems. It follows from the above that the

Examiner cannot generalize a problem met with a specific gene transfection, and should this problem occur, as evidenced above, it may be easily overcome with the aforementioned immunosuppressants.

Consequently, Applicants believe the presently claimed biological material is sufficiently described with regard to use as support for gene transfection. The new set of claims included in this Amendment are intended to cover:

I) A biological material wherein component (a) consists of at least one **autologous or homologous** cellular line selected from skin adnexa, germinative cells of hair bulb, endothelial and glandular cells, a process for its preparation and uses thereof.

II) An *in vitro* biological material containing at least one cellular line (homologous, heterologous, or autologous) selected from skin adnexa, germinative cells of hair bulb, endothelial and glandular cells, a process for its preparation and use thereof, for screening toxic substances.

Support for claim (I) amendments (in bold character) is found in the Specification at page 7 lines 17-21, at page 6 lines 30-31, and in the originally filed claim 6. Support for claim (II) amendments is the acknowledgment by the Examiner, originally filed claim 22 now claim 121, and in each Example in the Specification. Further, Applicants reserve the possibility to file a CPA or CIP for *in vivo* biological material containing **heterologous** cells and the uses thereof in skin, scalp transplants, for treating insufficient insulin production and liver transplants.

At page 8 of the Office Action, Claims 58-86 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Reconsideration is requested.

As requested, in new claims 87 and 109 the term "cellular type" was replaced with "cellular line". Support for this definition may be found at page 2, line 5. In new claims 87 and 109, "and" was inserted between "skin adnexa" and "germinative cells of the hair bulbs." In new claims 87 and 109 the definitions "part or all of the carboxy functions" were replaced with "part or all of the carboxylic groups of said hyaluronic acid", and partial or total hyaluronic esters" with "a hyaluronic acid ester having part or all of the carboxy groups of hyaluronic acid esterified with an alcohol of aliphatic,aromatic, arylaliphatic, cycloaliphatic series." Support for this amendment appears in WO96357207, page 4, lines 11-15 mentioned at page 6, line 1 of the present specification. In new claims 87 and 109, Applicants pointed out that the cellular line is seeded and grown on a biocompatible three dimensional matrix.

Support for this amendment may be found throughout the entire specification. In claims 61, 63, 83 and 85, now claims 90, 92, 112 and 114 we replaced "taken from" with "isolated". In claim 65, now new claim 94 and 116, we modified "and combinations" with "or combinations." In claim 67, now new claims 97 and 119 dependent from respective process claims 96 and 118, Applicants have pointed out that "keratinocytes are optionally seeded in association with skin adnexa and germinative cells of hair bulbs". Claim 68, now new process claims 98 and 120 depend respectfully from claims 88 and 110. In claim 85, now new claims 92 and 114, the phrase "sweat glands, hair bulbs and germinative cells are isolated has been changed to proper Markush format.

At page 9 of the Office Action, claims 58, 61, 62, 64, 65, 69-72 and 74-81 were rejected under 35 U.S. C. 102(b) as anticipated by Bellini et al (WO96/37519).

Reconsideration is requested.

Bellini discloses a polysaccharide hydrogel material consisting of a product derived from crosslinked hyaluronic or alginic acid esters, whose carboxylic groups are partially salified with an unsaturated aliphatic alcohol or araliphatic alcohol and the remaining groups are partially salified with an alkaline metal cation or with tetraalkylammonium. Unlike the present invention, in Bellini crosslinking is realized by treatment with UV, p and *y* radiations). The crosslinked product differs chemically from the hyaluronic acid derivatives used as support in the present invention, and specifically, they differ from the three dimensional hyaluronic acid esters of class (A) and the so called crosslinked inner esters of class (B) mentioned by the Examiner.

Applicants point out the following differences between the other features of Bellini and the present invention In Bellini, the hydrogel material is a derivative of a hyaluronic acid ester, not a three- dimensional hyaluronic acid ester such as that claimed in the present invention. Additionally, the polymer thus obtained has a molecular weight higher than the precursor hyaluronic acid ester having ethylenic unsaturation, since the ß and *y* radiations are able to initiate a radical polymerization involving the unsaturated bonds of the ester groups of hyaluronic acid, and the hyaluronic acid ester links to at least another molecule of hyaluronic acid ester by means of the unsaturation. Products having a different molecular weight also show different physical -chemical properties.

Neither can the hydrogel material obtained by crosslinking the hyaluronic acid ester with an unsaturated alcohol of Bellini be confused with the ester of class (B) in the biological material claimed in claim 87 and 109, where part or all of the carboxylic moieties

of hyaluronic acid are esterified with the hydroxylic groups of the same or a different hyaluronic acid chain. The chemical differences between the hydrogel material disclosed by Bellini and autocrosslinked material of the present invention is reflected by their vastly different physical structures. Bellini at page 3 lines 12-23, states "The new derivatives according to the present invention present a completely different structure from the previously described hyaluronic acid derivatives, such as hyaluronic acid, hyaluronic acid outer esters (USP4851521)(namely the hyaluronic acid esters of class (A)), its inner esters prepared as described in EP 341745 (namely the autocrosslinked hyaluronic acid ester of class (B)) as reported in Figure 1. Differences between the two hydrogels indicated as No.1 and No.2 are obvious. Indeed, while the gels constituted by inner esters of hyaluronic acid (No.2) are formed by microparticles of crosslinked polymers bound together by a simple physical- type bonds, the new compound (the hydrogel material) (No.1) present a compact three dimensional (wall to wall) structure. Therefore, the latter are characterized by a greater mechanical resistance.

The biological material as claimed in new claims 87 and 109 is novel and patentable over Bellini. Further, Bellini encompasses the use of different material for support from that disclosed in the present invention. Consequently, the present invention is patentable over Bellini.

At page 11 of the Office Action, claims 58, 65 and 66 were rejected under 35USC 103 (a) over Bellini et al. (WO 96/37519) in view of Cialdi et al (US Patent 6,027,741).

Reconsideration is requested.

The present invention represents a significant advantage over the prior art. As stated at page 2, lines 13-28 of the present specification, weak and fragile differentiated cells such as endothelial, glandular cells, islet of Langerhans, liver cells or skin adnexa are more difficult to isolate and culture onto artificial or plastic support than other types of cells like staminal cells, fibroblasts, and keratinocytes as they show poor proliferative properties and short survival times.

For example, liver cells can survive in vitro for about 7 weeks with less than 50% of the cells remaining viable, while skin adnexa last about two weeks, and islets of Langerhans just a few days. Although the properties of hyaluronic acid derivatives, in particular the hyaluronic acid esters namely the HY AFF matrices, are already known to favor the growth and development in vitro of resistant and very active cellular elements such as staminal cells or fibroblasts etc., an expert in the field would not have been able to predict that satisfactory

D2 proliferation rates and survival times can be achieved by cultivating the aforementioned weak and fragile cells on supports hyaluronic acid derivatives.

Bellini neither suggests nor teaches the presently claimed biological material, notwithstanding it discloses the use of a specific hyaluronic derivative as support for a series of cells. Bellini discloses a hydrogel material different from the hyaluronic acid derivatives encompassed in the instant invention; when compared to Bellini, the present invention discloses a biological material which is less compact and has less favorable physical properties. The hydrogel material of Bellini is not equivalent to that of the present invention.

Additionally, Bellini generically states that the specific hyaluronic acid derivative may be used as support for a long list of cells namely fibroblasts, keratinocytes, osteocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells. This does not suggest the presently claimed invention as no specific examples of such use are reported in Bellini. In fact, Bellini's generic affirmation does not differentiate between endothelial cells or Langerhan' s cells and other more stable cells such as fibroblasts osteocytes in terms of survival and stability on a hyaluronic acid derivative support.

In view of the foregoing, there is no expectation of success, that weak and fragile cells can grow efficiently and survive on a support made of a hyaluronic acid derivative, notwithstanding Bellini envisaged the mere possibility, not supported by experimental evidence, to use a particular hyaluronic acid derivative, obtained by crosslinking by UV, p and y radiation an unsaturated ester of hyaluronic as support for these cells and other more stable cells.

The biologic material of Bellini has physical properties decidedly better than those of some hyaluronic acid derivatives contained in the support of the biological material as claimed in the present application. Therefore, it follows that a skilled man in the art could not reasonably expect from Bellini's defective teaching, the use of different hyaluronic acid derivatives, with worse physical properties, could be advantageously and effectively used as support for cellular growth of weak and fragile cells, such as those contemplated in the presently claimed biological material.

Additionally, Bellini does not teach that the biological material may be in the form of a non woven tissue. This is not overcome by Cialdi. Cialdi discloses the sulfated derivative of class (C), one of the materials used as the support in the presently claimed material. Although Cialdi encompasses that said material is obtained in a three-dimensional structure, Cialdi

does not envisage use of said material as support for cellular components and does not suggest use thereof as support for the cells encompassed in the present invention.

Example 16 (14) mentioned by the Examiner discloses umbilical endothelial vein cells grown and proliferating in sulfated hyaluronic acid at a concentration of 5 mg/ml(second paragraph of Cialdi 's Example). The fact that endothelial umbilical vein cells in a medium containing dissolved therein sulfated hyaluronic acid proliferated, does not suggest that these materials could advantageously be used as a support in lieu of the hydrogel material of Bellini for cellular material, and in particular for endothelial cells. Example 14 represents a preliminary experiment for the purpose of verifying if sulfated hyaluronic acid inhibits cellular growth. Such preliminary results does not lead to a conclusion that not only the same cells used by Cialdi but also the other weak and fragile cells contemplated in the present invention, when seeded on the same material with a three dimensional structure, could grow and proliferate effectively.

In addition, another improvement over the prior art is that not only do cells grow and proliferate with the three- dimensional support as presently claimed, but more importantly, they have greater longevity as observed in Example 4 and Figure 3. Although Cialdi teaches that HUVEC grow and proliferate better in a medium containing sulfated hyaluronic acid, Cialdi is silent about the survival times of said cells in such a medium.

Consequently, the present invention could not be obvious from Bellini which discloses:

- a different hyaluronic acid derivative from those contemplated in the present invention with better properties in term of compactness than those of some hyaluronic acid derivatives disclosed in the present,

- envisaging among the possible uses of said different hyaluronic acid derivative, the use as support for a plethora of cells and among them also of some cells contemplated in the biological materials as presently claimed, however not giving any experimental evidence for such a use,

and in combination with Cialdi:

- disclosing sulfated hyaluronic acid derivatives, namely the hyaluronic acid derivative of class (C) encompassed in the instant invention, also in the form of a three dimensional material-teaching that HUVEC cells grow and proliferate in a medium containing a sulfated hyaluronic acid, but silent about use of said material as support for said type of cells or for other weak and fragile cells,

- HUVEC and other weak and fragile cells when seeded on said materials in the form of a three dimensional matrix survive longer than when seeded on plastic dishes.

Consequently, the presently claimed invention in unobvious over the above cited references.

At page 14 of the Office Action, claims 58-61 64-72 76-83 and 86 were rejected under 103(a) over Soranzo (WO 96/33750) in view of Cialdi, Bellini, and Dorigatti et al (U.S. 5,520,916).

Reconsideration is requested.

Soranzo' s artificial skin comprises rather a complex system formed by an upper microperforated membrane based on a hyaluronic acid derivative on which keratinocytes have been seeded and left to proliferate and an underlying non-woven tissue based on a hyaluronic acid derivative wherein fibroblasts have been seeded and left to proliferate(see the abstract, description page 5, 1ines 12-16 and claim 1).

Soranzo' s skin differs from the presently claimed biological material in both the type of supports and the cellular components. Soranzo' s skin contains two different types of supports, depending on the contemplated specific cellular components; for keratinocytes, a perforated membrane (a two dimensional support) based on a hyaluronic acid derivative; whereas for fibroblasts, a non woven three-dimensional matrix based on a hyaluronic acid ester,

Conversely, according to the present invention, only three-dimensional supports (see for a further demonstration new claims 94 and 116), of a hyaluronic acid derivative selected from the classes (A) -(E) are claimed. Additionally, the artificial skin encompassed in Soranzo contains only two types of cellular components; its outer layer contains keratinocytes whereas the inner layer contains fibroblasts.

The biological material according to the presently claimed invention contemplates as cellular components at least one cell type selected from the group consisting of endothelial cells glandular cells, skin adnexa (sebaceous glands and sweat glands cells). Keratinocytes and fibroblasts are optional cellular components (see claim 88, 89, 110 and 111). Therefore, in view of the foregoing, Soranzo does not suggest the presently claimed biological material.

Soranzo teaches away from the presently claimed biological material, because it is essential to dispose as support for the cellular components of a combination of a three-dimensional matrix with a bidimensional matrix, whereas in the presently claimed invention only three-dimensional supports are contemplated.

At page 12, lines 19-27 Soranzo teaches that artificial human skin keratinocytes migrate through the micropores in the membrane, to the upper part of the non-woven tissue in direct contact with the membrane. Soranzo's purpose is the achievement of an artificial human skin simulating both the epidermal and dermal layer of the natural one, wherein both fibroblasts and keratinocytes are present, both types actively proliferating and separated at the interface, by the protein extracellular matrix, having the characteristic of a dermo-epidermal junction (page 5 lines 5-10). This purpose is achieved via keratinocyte migration through the micropores in the membrane to the upper part of the non-woven tissue in direct contact with the membrane, while the fibroblasts produce a considerable quantity of protein extracellular matrix. It follows that keratinocytes embedded in the non-woven tissue, in direct contact with fibroblasts, take on the appearance of epitheloid basal cells. Soranzo at most suggests that only in the upper part of the non woven tissue fibroblasts and keratinocytes are contemporaneously present, resembling the epithelial basal layer. Such a teaching does not suggest the possibility of overcoming the drawbacks associated with the weak and fragile cells like those present in the biological material as presently claimed, by cultivating and growing such cells on a support containing a hyaluronic acid derivative selected from those contemplated in the aforementioned classes (A)-(E), and wherein fibroblasts and keratinocytes are moreover optional cellular components.

Applicants further point out that the aforementioned Soranzo ' s deficiencies could not be overcome by Dorigatti's disclosing the process for preparing non woven tissue made of hyaluronic acid esters. Dorigatti does not suggest or disclose possible uses of said material is encompassed the use as support for cellular components. The addition of Dorigatti does not add anything more than that already contained in Soranzo, whose teaching not only fails to suggest the instant invention, but actually teaches away from it.

Further, Soranzo and Dorigatti deficiencies are not overcome by Cialdi.

Cialdi does not suggest the use of said material as support for cellular components, and suggests the use thereof as support for the cells encompassed in the present invention. Cialdi's very preliminary result does not lead to the conclusion that weak and fragile cells contemplated in the present invention, when seeded on the same material with a three dimensional structure, grow and proliferate effectively. Additionally, Cialdi is silent about the survival times of said cells in such a medium.

The purpose of Example 15 (not 16) mentioned by the Examiner is to verify if the complex Cu(II) with sulfated hyaluronic acid has angiogenetic effect like the complex Cu(II)

-heparin (see the first paragraph of said example). The ability of sulfated hyaluronic acid to induce angiogenesis in vitro involves a cell migration method and it consists in determining the number of endothelial cells that preferentially migrate towards the test sample rather than control sample (see column 13 lines 23-32). The results indicate that (see column 13 line 59 and column 14 line 3) that the complex (Cu{ll) -sulfated hyaluronic acid is capable of inducing angiogenesis *in vitro* to an extent similar to that of the complex Cu {II) heparin, whereas there is a preferential migration by endothelial cells towards Cu(II) sulfated hyaluronic acid rather than towards sulfated hyaluronic acid. By analogy, there is a preferential migration towards the heparin complex rather than uncomplexed heparin.

It follows from the above that the hyaluronic acid has angiogenic effect only when in the form of a complex with Cu(II) and not if it used as a support in an uncomplexed form such as in the presently claimed biological material.

Cialdi's teaching that only in combination with Cu(II) the sulfated hyaluronic acid has angiogenic properties teaches away from the presently claimed biological material, encompassing the use of sulfated hyaluronic acid as such. Therefore, Cialdi is completely unable to overcome the Soranzo and Dorigatti deficiencies.

The addition of Bellini which has been distinguished *supra* does not suggest the presently claimed invention. Bellini's hydrogel material is a derivative of a hyaluronic acid ester, and not a three-dimensional matrix comprising a hyaluronic acid ester as such, like that contemplated in the biological material as presently claimed in claim 87 and in claim 109 of class (A).

In addition, the polymer thus obtained has an average molecular weight higher than the precursor hyaluronic acid ester having ethylenic unsaturation, since the ß and y radiations are able to initiate a radical polymerization involving the unsaturated bonds of the ester groups of hyaluronic acid, and the hyaluronic acid ester links to at least another molecule of hyaluronic acid ester by means of the unsaturation. It follows from the above that products having a different molecular weight also show different physical-chemical properties, and therefore cannot be considered an obvious variation of the three dimensional hyaluronic acid ester disclosed in (A). Further, Bellini's hydrogel material cannot be considered an obvious chemical equivalent of the autocrosslinked derivative of class (B).

In addition the chemical difference between the hydrogel material disclosed by Bellini and the autocrosslinked material also reflects on the structure of said compounds since as evidenced by the same Bellini the hydrogels presents a completely different structure from the previously described hyaluronic acid derivatives, such as hyaluronic acid, hyaluronic acid outer esters (USP4851 521)(namely the hyaluronic acid esters of class (A), its inner esters prepared as described in EP 341745 (namely the autocrosslinked hyaluronic acid ester of class (B)) as reported in Figure 1. Indeed while the gels constituted by inner esters of hyaluronic acid (No.2) are formed by microparticles of crosslinked polymers bound together by a simple physical-type bonds, the new compound (the hydrogel material) (No.1) present a compact three dimensional structure (wall to wall). The latter, are therefore, characterized by a greater mechanical resistance.

Finally, Bellini simply and generically states that the specific hyaluronic acid derivative may be used as support for a long list of cells namely fibroblasts, keratinocytes, osteocytes, stem cells, endothelial cells, Kupfer's and Langerhans cells. The above sentence although as no specific examples of such a use is reported in said reference. Such a statement in the absence of experimental tests at most suggests the endothelial cells, Langerhan' s cells had equivalent properties in term of survival and stability on a hyaluronic acid derivative support to those of the other more stable cells such as fibroblasts osteocytes, etc mentioned by Bellini. However, this teaching was in substantial contradiction, with what was widely known (see in this regard the plethora of prior art mentioned at the aforementioned page 2 lines 13-28, reciting that all the type of cells contemplated in the presently claimed biological material result very weak and fragile and are characterized by having very short survival times, when cultivated on a plastic sheet).

In view of the foregoing, Bellini does not overcome the Soranzo, Dorigatti and Cialdi deficiencies. The present invention is in no way obvious over Soranzo, in view of Dorigatti, Cialdi and Bellini.

It follows from the above that the generic teaching contained in this reference concerning a possible use thereof as support for cellular components, could in no way suggest that the process as claimed in claim 67 allowed to obtain a biological material wherein the

aforementioned weak and fragile cells could grow and proliferate effectively and could survive longer than on conventional supports.

The Applicant respectfully submits that the present invention represents an improvement over the prior art. Further, the Applicant respectfully submits that all the claims are in a condition for allowance.

Early and favorable action is earnestly requested.

Respectfully submitted,

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